Developing Next-Generation Drugs from Designer Proteins

Many cancers are difficult to treat due to challenges in targeting proteins that drive cancer development. The Myc/Max transcription factor is such a target that it is associated with >70% of cancers. One promising avenue is to design Myc/Max mimics that inhibit the Myc/Max transcription factor from binding its DNA target, which is the E-box. The Myc/Max protein structure, the basic/helix-loop-helix/zipper (bHLHZ), inspired us as our design scaffold. Building upon our successful Myc/Max protein mimics, particularly **MEF**, we aimed to enhance MEF's E-box binding specificity and affinity by introducing intrinsically disordered regions (IDRs). We hypothesized that incorporating IDRs into the loop of the helix-loop-helix region would optimize MEF's selective targeting of the E-box, as we found in earlier designed proteins. This project involves two key phases: evaluating the IDR loop as an independent module that enhances E-box binding and exploring the impact of loop length and sequence on MEF's selectivity for the E-box. By employing bacterial one-hybrid assay and fluorescence anisotropy, we aim to create next-generation protein drugs exclusively targeting the Myc/Max/E-box network, thereby offering a unique strategy against undruggable cancers.